A CONTRIBUTION TO THE STUDY OF THE MYELIN DEGENERATION OF THE PULMONARY ALVEOLA EPITHELIUM.

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In 1854 Virchow (1) described as "myelin drops" a substance which he found in several tissues of the human body. Nearly twenty years later Buhl described a similar substance in the pulmonary alveolar cells, and attached much importance to its presence. A few other investigators have referred to alveolar cells containing this substance in the sputum of both healthy and diseased individuals, but the conclusions which have been reached are so widely separated that further observations are necessary to complete our knowledge of this interesting metamorphosis. The only fact which seems to be fully established concerning it is that under certain conditions, which have not been clearly defined, these cells undergo a very peculiar change, which was designated by Buhl as *myelin degeneration*, on account of the resemblance of the resultant substance to the drops of myelin which escape from the cut ends of nerve fibers. The fact has not heretofore been clearly determined whether these cells are subject to this change while they are still attached to the alveolar wall or whether it is a process peculiar to their dissolution, induced after they are separated from their source of nutrition. The simple fact has been observed that in the alveolar cells that are found in the sputum this degeneration is sometimes present. Its importance is somewhat speculative, although several opinions have been expressed concerning its significance.

Buhl (2) considered the myelin degeneration of the alveolar cells to be of special value in the diagnosis of desquamative pneumonia and in differentiating it from fibrous pneumonia, which it resembles in many particulars. Bizzozero (6) and Guttmann and Smidt (5)

found alveolar cells undergoing this change in the sputum of healthy individuals, especially in those who had passed the age of thirty. Senator (7) has reported finding these drops in the cells from the deep layers of the bronchial epithelium. Hoffmann (8) and Lenhartz (9) considered them of diagnostic importance in valvular trouble of the heart on account of the blood pigment which they frequently contain. Sommerbrodt (3) and Krönig (10) agree essentially with Hoffmann in his views of their diagnostic importance.

Degenerating Alveolar Cells and their Products in Sputum.

In the fall of 1891 I had occasion to examine several specimens of sputum from a married lady, aged about thirty years, who was suffering from pulmonary tuberculosis. In the examination of the sputum in the fresh* condition my attention was directed in addition to the elements usually found in tubercular sputum to a considerable number of large, squamous cells, varying in size from two to four times that of leucocytes. They were finely or more coarsely granular, and in some instances they contained within the cellular substance several quite large, round, or pear-shaped bodies. There were also a large number of free bodies in the sputum, varying in size from mere points to 20 μ in diameter. They were round, pear-shaped, pointed, and irregular in form, and of a homogeneous, neutral gray, or pearly appearance. A few of the larger forms exhibited a stratified condition. Usually they presented a double contour, and resembled somewhat closely the myelin drops found in teased preparations of nerve tissue. Up to that time I had considered these cells and free bodies, which had occasionally been observed, as cells undergoing fatty degeneration and fat globules. In these examinations I became convinced that these bodies were not the product of fatty changes, and their interpretation occasioned no little study. Finally, the cells were identified with the alveolar

*Attention should be called to the importance of examining sputum in a fresh condition. There are, to be sure, specific methods by which particular objects are demonstrated, as, for example, tubercle bacilli, but in the examination for the bacilli only many other structures may be destroyed, and consequently entirely escape the attention of the observer. The value of examining microscopically tissues in a fresh condition seems to be overlooked by a large number of microscopists, who rely upon the examination of stained preparations only.

cells described by Buhl, and the free bodies were found to be the product of the myelin degeneration of the alveolar cells. The specimens of sputum that were subsequently examined contained an innumerable number of these forms. Tubercle bacilli were present in large numbers. The patient was sent to the mountains, where she improved, but nearly two years later (spring of 1893) the sputum contained these bodies in large numbers.

Further examination of the alveolar cells in tubercular sputum showed them to be present in four forms: (1) cells varying from 10 to 15 μ in diameter, with the cellular protoplasm finely granular and the nuclei distinct; (2) cells similar to (1) but containing more or less pigment; (3) cells slightly larger than (1) and filled with small bright bodies with or without pigment, nuclei not distinct; and (4) cells very much larger, 30 to 40 μ in diameter, and filled with small and much larger bodies of a high refractive index, and the nuclei entirely obliterated. The forms described under (1) and (2) were differentiated from other epithelial cells by their size and form, and those designated under (3) and (4) by their size and the character of the bodies which they contained. Bizzozero speaks of fatty alveolar cells, but in my investigations the bright bodies within these cells have not reacted to the reagents for fat globules although they resembled them very closely in their microscopic appearance. Where the myelin degeneration was more advanced the cells were frequently broken down and the myelin bodies were observed escaping from them. The pigment is either of an extraneous nature, such as fine particles of coal, iron dust, or other pigmentary substances that were inhaled during respiration or to the pigment from the blood. I have observed the pigmented cells a few times only and in all of these cases it was evidently of an extraneous character.

The free bodies in the sputum are exceedingly interesting from the great variety of forms and sizes which they display. Frequently they give the appearance of a band of grayish, homogeneous substence wound and twisted into a variety of forms. The round forms appear with a uniform rather thick periphery and a central marking which at times resembles a perforation. In the pear-shaped and pointed forms there is almost invariably a central longitudinal marking. In some of the larger homogeneous bodies the beginning of a laminated condition was observed. In other cells it was more

advanced, and in still others the lamination was nearly complete. In watching these bodies for a little time they were observed to change their form. In the larger homogeneous bodies the change resembled somewhat closely the amœboid movement, but it was undoubtedly due to a passive motion produced in the flexible, elastic bodies by the action of currents in the preparation, or by the pressure of the cover-glass. In the stratified forms there were frequently observed quite jerky or springy movements of the laminæ. The lamination and subsequent breaking up of the laminæ appear to be the last stages in the degeneration of the cells. The source of the large forms is explained on the supposition that in the metamorphosis of the cells the small bodies usually observed coalesce, forming one or more large masses. A few cells have been observed which contained these large bodies.

The Reaction of the Degenerating Alveolar Cells to Micro-chemical Re-agents.

The myelin bodies either free or within the epithelial cells, do not react readily to the ordinary micro-chemical re-agents. In a preparation of sputum (prepared by placing a drop on a slide and covering it with a cover-glass) the large alveolar cells and free bodies can be readily observed by the aid of a 4 mm. objective. If to the preparation a few drops of a 10 per cent. solution of potassium hydrate is added (allowed to pass under the cover-glass), the mucous substance is dissolved and the free myelin-drop-like bodies stand out very clearly. The larger alveolar cells are disintegrated and the contained bodies set free. This is the most valuable reagent which I have found in studying these forms. The myelin bodies are rapidly destroyed by alcohol, less quickly with weak acids. They do not take any of the stains ordinarily used in histological or bacteriological work. Osmic acid produces a very faint brownish color. Kaatzer (11) found osmic acid to produce a deep black color. In sputum that has stood for some time (several weeks in a cool place), iodine in iodide of potash (iodine, 1 gramme; iodide of potash, 2 gammes; distilled water, 300 cc.) imparts a faint lemon color to the homogeneous forms. This color is not changed by the addition of sulphuric acid. They are affected slowly by ether. The fact that they are destroyed by alcohol renders their demonstration in mounted lung tissue practically impossible. In sputum

hardened* in picric-acid-alcohol, imbedded in paraffin and sectioned, I have been able to detect these bodies in a much shrunken condition, but they are not satisfactorily demonstrated in this way. Their identity with myelin is not yet positively established, but so far as I have been able to determine, they resemble it more closely than any of the other substances that have been found in the animal body. Until the chemical nature of this substance is more accurately determined, it seems best to adopt the term introduced by Buhl. Future investigations, however, may demonstrate that it is not so closely related to myelin as we now think it is, and consequently the term myelin degeneration may have only a temporary existence.

The very large number of degenerating alveolar cells in the specimens of tubercular sputum from the individual mentioned led to a somewhat careful search for these cells in all other specimens which I have had occasion to examine. They have appeared in over 90 per cent. of these specimens. In several instances they could not be found in the first specimens received, but in subsequent specimens they were present. Occasionally they could be found in only one or two preparations from a large number made from the same specimen. I have also found them in large numbers in several specimens of sputum in which no tubercle bacilli could be found, but in which there was much pus and many spheroidal (basement) epithelial cells from the bronchi. I have also found them in the sputum of people suffering from a slight cough (bronchitis), and in a few specimens from people twenty-five years of age and older, who were believed to be perfectly healthy.

Through the kindness of Dr. Wellington (at that time resident physician at the Children's Hospital, Washington, D. C.), I obtained lung tissue from a few fatal cases of tuberculosis. A most interesting case was one of general tuberculosis in a girl about six years of age. There were comparatively few tubercles in the lungs. They were small, and in the piece which I received they were separated from each other by a distance of from 2 to 5 cm. The inter-

*In an article on the technique and value of sputum examination (*Medical News*, May 14, 1892) I called attention to the value and described the technique of sectioning sputum for the study of the relation of the tubercle bacilli to the yellowish more dense masses in the sputum. Although this method cannot be recommended for the demonstration of tubercle bacilli, it is possessed of certain advantages for the histological study of sputum.

vening tissue was apparently normal. The alveolar epithelium from near the tubercles and from the intervening normal tissue was very carefully examined. In many of the alveolar cells from near the tubercles there were myelin bodies varying in diameter from 0.2 to 4.0 μ. When treated with potash the cells were disintegrated and the enclosed bodies set free. They could not be distinguished from those found in sputum. In the tissue most remote from the tubercles the alveolar cells rarely contained the myelin bodies, although they were occasionally observed. This is interesting, as in the tissue immediately adjoining the tubercle almost every cell was undergoing this degeneration. All of the cells were not detached from the alveolar wall. Like the sputum, these bodies could not be detected in sections of the lung hardened in alcohol.

Myelin Degeneration of Alveolar Epithelium in Animals.

The appearance of these bodies in the alveolar cells of the human lung led to the examination of the lungs of different animals. In pigs, rabbits, guinea pigs, and mice that perished from swine plague, hog cholera, or other virulent bacteria the myelin degeneration of the alveolar cells was demonstrated by the aid of a 10 per cent. potash solution in all of the cases examined. The technique necessary to bring out these myelin drops was very simple. Sometimes they could be seen very clearly when a bit of the lung tissue was teased in normal salt solution. Usually, however, it was necessary to add to the preparation a few drops of the solution of potassium hydrate which would dissolve the cellular substance and leave the minute and larger myelin bodies free. These were usually pointed or pear-shaped and exhibited the longitudinal marking. They differed in no appreciable manner from those found in the human lung or sputum. In healthy animals that were killed by bleeding or chloroform very few of the alveolar cells were found to contain these drops. Frequently they could not be found at all. In lungs that were not examined for from 2 to 3 days after the death of the animal the myelin degeneration of the alveolar cells was more common. In lungs of cattle affected with pleuro-pneumonia, Dr. Theobald Smith found the alveolar cells to contain bodies which presumably were the same as those which I have found in other animals. They differed, however, in being more uniform in size. In 1890 I observed similar forms in the alveolar cells of a cow's

lung which contained actinomycosis and a small amount of accompanying pneumonia, but at that time their nature was not determined.

From my observations the myelin degeneration of the alveolar epithelial cells may be looked for, (1) in the sputum of people suffering from pulmonary tuberculosis and certain other more or less serious lung disturbances; (2) in the lungs of certain species of animals (and probably in all mammals) that have suffered from a disease in which there was more or less fever before death, either with or without a localization of the disease in the lungs (the more the lungs are affected the more numerous are the myelin drops); and (3) in the sputum of people of twenty-five years of age or older and in the lungs of healthy animals. In these, however, the myelin degeneration is more rarely found, and the number of cells undergoing this change are very few compared with the number in the diseased lungs. This would indicate that the myelin degeneration is the course through which the pulmonary alveolar cells naturally pass in their final disintegration, but that it is hastened by the influence of certain diseases. Virchow (1) found myelin drops in the various organs of the body, and Panizza (4) found them to be a product of the mucous membrane of the mouth of frogs. With these exceptions, they appear to have been observed only in the pulmonary alveolar epithelium. Panizza considered the myelin drops to be a product of mucin. The appearance of this metamorphosis in the alveolar cells of such a large number of animals indicates its universality, and points out another interesting condition which may be studied in the lower animals, and about which much may be learned without waiting for the accumulation of facts from the human species. Although I have examined the lungs of a large number of animals under the conditions previously stated, other work has prevented a more exhaustive study of the conditions under which this metamorphosis occurs.

My opportunities have not been such that I could accumulate data upon the practical or diagnostic value of these peculiar cells in the human sputum. It is hoped that those who have clinical advantages will make good use of their material and microscopes, so that in the near future the diagnostic value or non-significance of these forms may be clearly established. It is probable, however, that they will be found in a large variety of inflammatory affections of the lungs, but it is not impossible that they may be, to a limited extent, of diagnostic value, especially in young patients.

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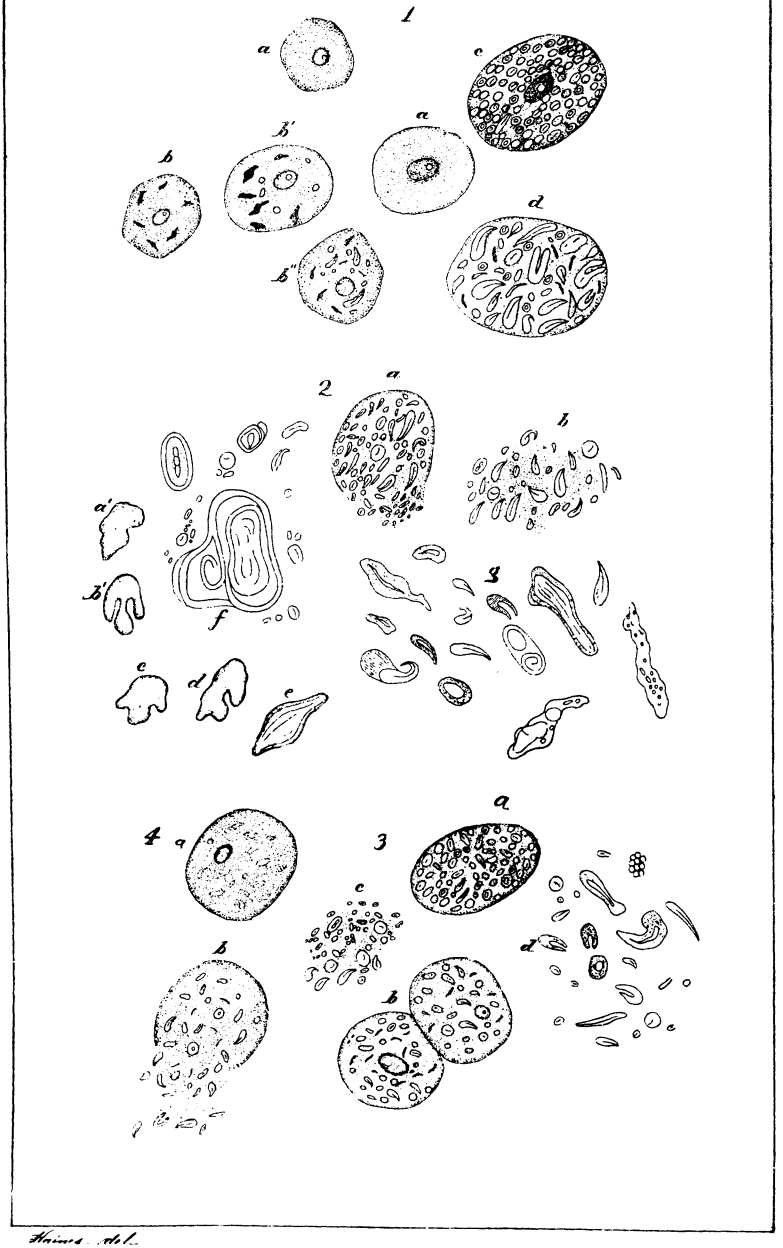
Description of Plate.

The figures in the plate are to illustrate the alveolar epithelial cells and a few of the free bodies resulting from their myelin degeneration. They were made from preparations of human sputum, and from the lungs of a guinea pig and rabbit which died from hog cholera. Bodies not distinguishable from those found in the alveolar cells of the guinea pig's and rabbit's lungs were found in the lungs of the other animals mentioned in the text. The drawings were made with the aid of a Zeiss apochromatic objective, 2 mm., 1.30 n. a., and the measurements were made with the compensating micrometer ocular No. 6. Each micromillimeter is represented by a millimeter, thus giving a magnification of a thousand diameters.

FIG. 1.—Alveolar epithelial cells from human sputum: *a*, normal; *b*, *b'*, and *b''*, pigmented cells; *b''*, contain myelin bodies in addition to the pigment; *c*, alveolar cells containing round bodies resembling fat globules, and *d*, large alveolar cells containing numerous forms of myelin bodies.

FIG. 2.—Alveolar cell and free myelin bodies found in human sputum (tuberculous); *a*, an alveolar cell containing myelin bodies immediately after the addition of a ten per cent. potash solution; *b*, the same cell after it had been disintegrated by the action of the solution of caustic potash and before the myelin bodies had become disseminated; *a'* to *g*, free myelin bodies observed in sputum; *f* represents one of the large free myelin bodies in a highly laminated condition, the lines indicating the laminæ, which were constantly changing and breaking at the time the drawing was being made. The other figures illustrate some of the forms that are usually present in preparations of tuberculous sputum. *a'*, *b'*, *c*, *d*, and *e* are drawings of one of the larger homogeneous masses of myelin and a few of the different shapes it assumed within a period of ten minutes; *a'*, the form as first observed, *b*, *c*, *d*, and *e*, the four con-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secutive forms through which it passed (movement passive); in *e* the striæ can be detected; *f* appears to be the last stage of these bodies before their complete dissolution. In fresh preparations of tuberculous sputum treated with the potash solution all of these forms can frequently be observed.

FIG. 3.—Alveolar cells and the degenerated forms from the lung of a guinea pig which perished from hog cholera; *a* and *b*, alveolar cells treated with a weak solution of potassium hydrate; *c*, the same cell (*a*) after the action of a ten per cent. potash solution; *d*, represents free myelin bodies in the preparation after the action of the potash.

FIG. 4.—An alveolar cell from the lung of a rabbit which perished from hog cholera. The tissue was teased in normal salt solution; *a*, before the addition of the potash solution; *b*, after the action of potash, but before the entire cellular substance was destroyed.